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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/164,568	10/01/1998	RANDOLPH J. NOELLE	012712-572	6823

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EXAMINER	
GAMBEL, PHILLIP	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 01/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/164,568	NOELLE ET AL.	
	Examiner	Art Unit	
	Phillip Gambel	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 September 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *82-94* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *82-94* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment, filed 9/23/05, has been entered.
Claims 1-81 have been canceled.
Claims 82-94 have been added.

Claims 82-94 are pending and being acted upon presently.

2. This Office Action will be in response to applicant's amendment, filed 9/23/05.
The rejections of record can be found in the previous Office Actions.

3. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Given applicant's canceled claims 63-64, the previous rejection under 35 U.S.C. § 112, first paragraph, written description, has been withdrawn with respect to the recitation of "peripheral blood activated B lymphocyte" (claim 63) and "bone marrow activated B lymphocyte" (claim 64).

5. Applicant's amendment filed 3/2/05, has obviated the previous objection to the specification to recite the appropriate depository information.

6. Applicant's amendment filed 9/23/05, concerning defining the recited antigen by its binding to CD40Ig as featured (i)-(iii) which provides a fully characterized antigen which adequately defines the anti-gp39 antibody genus of step (b) in conjunction with Noelle v. Lederman, 355 F.3d 1343, 1349-1350 (Fed. Cir. 2004) is acknowledged.

However, in contrast to applicant's assertions of reciting a fully characterized antigen in the newly added claims,
rejections under 35 USC 112, first paragraph, written description and enablement are set forth herein.

Also, in contrast to applicant's assertions that the claims are directed to methods of reducing T cell responsiveness,
the claimed methods depend upon finding "an antigen which is bound by a CD40-Ig fusion protein, is present on activated by not resting T cells and has the same molecular weight as a protein precipitated by CD40-Ig fusion protein".
Without a more precise definition of the claimed antigen specificities, the skilled artisan cannot practice the claimed method of treatment. It means little to invent a method if one does not have possession of the "antigens" that are essential to practice the method. Without possession of the claimed genus or a representative number of species to satisfy the claimed genus of antigen(s), the claimed endpoints are illusory and there is no meaningful possession of the method.

7. This is a rejection under 35 USC § 112, first paragraph, "written description" (and not new matter).

Claims 82-94 are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed.

There is insufficient written description encompassing the claimed "antigen" specificity because the relevant identifying characteristics such as structure of other physical and/or chemical characteristics of the claimed "antigen" recited in claim 82(b)(i)-(iii) or "a protein precipitated by the CD40-Ig fusion protein" recited in claim 82(b)(iii) (i.e. "CD40L" or "gp39") are not set forth in the specification as filed, commensurate in scope with the claimed invention.

The claimed methods may depend, at most, upon finding "an antigen which is bound by a CD40-Ig fusion protein, is present on activated by not resting T cells and has the same molecular weight as a protein precipitated by CD40-Ig fusion protein" or "a protein precipitated by the CD40-Ig fusion protein".

Applicant had submitted that at the time of filing of the instant application, the human T cell antigen gp39 has been described in Hollenbaugh et al. (EMBO J 11: 4313-4321, 1992).

However, the claims are not limited to the known CD40L molecules known at the time the invention was made, nor disclosed in the specification as filed (e.g., see page 2, paragraph 3 and page 7, paragraph 1 of the instant specification application as filed.

Applicant's reliance upon the holdings of the Federal Circuit in addressing the written description of CD40L/gp39/CD40CR in Noelle v. Lederman, 69 USPQ2d 1508 (CAFC 2004) is noted (see applicant's Amendment, filed 9/23/05).

However, applicant was not in possession of the necessary common attributes possessed by antibodies that bind to the "antigen" and "a protein" recited in the instant methods, currently recited is not consistent with the requirements under 35 USC 112, first paragraph, written description as well as the holdings of the Federal Circuit in addressing the written description of CD40CR in parent application USSN 07/742,480. See Noelle v. Lederman, 69 USPQ2d 1508 (CAFC 2004).

For example, the instant claims do not recite the art recognized terms or designations of the "antigen" or "a protein" (e.g. CD40 ligand) in the claimed methods.

Rather, the claims are drawn to any "antigen which is bound by a CD40-Ig fusion protein, is present on activated by not resting T cells and has the same molecular weight as a protein precipitated by CD40-Ig fusion protein" or any "protein precipitated by the CD40-Ig fusion protein".

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483.

Applicant is relying upon certain biological activities and the disclosure of the limited representative species of certain known CD40 ligands disclosed on page 2, paragraph 3 and page 7, paragraph 1 of the instant specification to support an entire genus of "antigens" and "proteins" as it reads on any CD40-Ig binding protein found in any mammal and which are not limited to those known CD40 ligands at the time the invention was made and relied upon the instant disclosure as filed.

The instant invention encompasses any "antigen" and "protein" defined by the characteristics of claim 82 (i)-(iii) as a target of the instant methods, yet the instant specification does not provide sufficient written description as to the structural features of said genus of "antigens" and "proteins" and the correlation between the chemical structure and the function of the genus of "antigens" and "proteins".

While applicant relies upon the disclosure of the known CD40 ligands at the time the invention was made to claim a broad genus of "antigens" and "proteins" not described in the specification as filed.

The specification does not disclose sufficient procedures that will necessarily lead to discovery for a genus of "antigens" and "proteins" broadly encompassed by the claimed invention and it does not identify a sufficient number of representative members of such "antigens" and "proteins", other than those CD40 ligands known at the time the invention was made.

The application does little more than describe the desired function of the claimed genus of "antigens" and "proteins" broadly encompassed by the claimed invention and does not contain sufficient information by which a person of ordinary skill in the art would understand that the inventors possessed the claimed invention.

The instant specification does not provide either for the isolation or written description of "antigens" and "proteins" other than the known CD40 ligands.

Mere idea or function is insufficient for written description; isolation and characterization at a minimum are required.

Further, Skolnick et al. (Trends in Biotech. 18: 34-39, 2000) teach that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (e.g., "Abstract" and "Sequence-based approaches to function prediction", page 34). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see in particular "Abstract" and Box 2).

In the absence of sufficient guidance and direction to the structural and functional analysis, applicant's reliance upon the known CD40 ligands disclosed in the specification as filed does not appear to provide sufficient written description of a genus of distinct molecules of "antigens" and "proteins" broadly encompassed by the claimed invention.

The Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, & 1 "Written Description" Requirement make clear that if a claimed genus does not show actual reduction to practice for a representative number of species; then the Requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 column 3).

Further, it is noted that the co-inventor's related application USSN 08/742,480 was party to an Interference with the United Stated Patent and Trademark Office Board of Patent Appeals and Interferences (Interference No. 104,415). See Noelle v. Lederman, 69 USPQ2d 1508 (CAFC 2004).

With respect to the disclosure of antibodies that bind a genus of CD40CR antigens, including human CD40CR; the Court affirmed the decision by the Board supported by substantial evidence and the law which held that the USSN 08/742,480 application lacked written description for the genus of CD40CR antigens, including human CD40CR antigen.

Given the state of the art in the early 1990's described by the expert witnesses and evidence, the Court also affirmed the decision by the Board by finding that one skilled in the art would have lacked a reasonable likelihood of success in isolating human CD40CR antigen given mouse CD40CR antigen, including consideration of Noelle's reliance on various screening methods disclosed in the specification.

Applicant has not disclosed "a fully characterized antigen / protein" as it reads on the genus of "antigens" or "proteins" encompassed by the claims other than those CD40 ligands known at the time the invention was made and relied upon the disclosure as filed.

In the absence of structural characteristics that are shared by members of the genus of "antigens" and "proteins"; one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, applicant was not in possession of the claimed genus. See University of California v. Eli Lilly and Co. 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997).

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, & 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

8. Claims 82 -94 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for "the known CD40 ligands disclosed on page 2, paragraph 3 and the page 7, paragraph 1 of the instant specification,
does not reasonably provide enablement for
any "antigen having the characteristics recited in instant claims 82 (b)(i) – (iii)" OR
any "protein precipitated by the CD40-Ig fusion protein" recited in claim 82(b)(iii).

The specification does not enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to make and use the invention commensurate in scope with these claims.

Applicant has not provided sufficient biochemical information (e.g. molecular weight, amino acid composition, N-terminal sequence, etc.) that distinctly identifies the genus of "antigens" or "proteins" as the target specificity of the claimed methods.

Applicant has not enabled the breadth of "antigens" or "proteins" targeted by the antibodies in the claimed methods because the relevant identifying characteristics such as structure of other physical and/or chemical characteristics of the claimed "antigen" / "protein" (i.e. "CD40L" or "gp39") are not set forth in the specification as filed, commensurate in scope with the claimed invention.

The claimed methods may depend, at most, upon finding "an antigen which is bound by a CD40-Ig fusion protein, is present on activated by not resting T cells and has the same molecular weight as a protein precipitated by CD40-Ig fusion protein".

Applicant had submitted that at the time of filing of the instant application, the human T cell antigen gp39 has been described in Hollenbaugh et al. (EMBO J 11: 4313-4321, 1992).

However, the claims are not limited to the known CD40L molecules known at the time the invention was made, nor disclosed in the specification as filed (e.g., see page 2, paragraph 3 and page 7, paragraph 1 of the instant specification application as filed.

For example, the instant claims do not recite the art recognized terms or designations of the "antigen" and "protein" (e.g. CD40 ligand) in the claimed methods.

Rather, the claims are drawn to any "antigen which is bound by a CD40-Ig fusion protein, is present on activated by not resting T cells and has the same molecular weight as a protein precipitated by CD40-Ig fusion protein" or any "protein precipitated by CD40-Ig fusion protein".

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth.

The specification does not describe nor enable any "antigen" / "protein" broadly encompassed in the claimed methods.

Applicant appears to be relying upon certain structural and biological activities of the known CD40 ligands (see page 2, paragraph 3 and page 7, paragraph 1 of the instant specification) to support an entire genus of "antigens" / "proteins" and which said "antigens" / "proteins" are not limited to the known mammalian or human CD40 ligands at the time the invention was made and relied upon by the specification as filed.

The instant claims encompass any "antigen which is bound by a CD40-Ig fusion protein, is present on activated by not resting T cells and has the same molecular weight as a protein precipitated by CD40-Ig fusion protein" or any "protein precipitated by CD40-Ig fusion protein",
yet the instant specification does not provide guidance on how to make and how to use the essential structural features of said genus of "antigens" / "proteins" and the correlation between the chemical structure and the function of the genus of "antigens" / "proteins", broadly encompassed by the claimed methods.

The instant disclosure does not set forth sufficient procedures that will necessarily lead to discovery for such "antigens" / "proteins" broadly encompassed by the claimed invention and it does not identify a sufficient number of representative members of such "antigens" / "proteins", other than the known CD40 ligands at the time the invention was made.

The application does little more than describe the desired function and some limited ill-defined structure of the claimed genus of "antigens" / "proteins" broadly encompassed by the claimed invention and does not contain sufficient information by which a person of ordinary skill in the art would be able to make and use the scope of "antigen specificities" / "proteins" broadly encompassed by the claimed invention, other than those CD40 ligands disclosed in the specification as filed.

For example, applicant has not isolated or taught how to make and use any "antigen" / "protein" other than those disclosed in the specification as filed.

Further, Skolnick et al. (Trends in Biotech 18: 34-39, 2000) teach that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (e.g., "Abstract" and "Sequence-based approaches to function prediction", page 34). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see in particular "Abstract" and Box 2).

In the absence of sufficient guidance and direction to the structural and functional analysis, applicant's reliance upon the known CD40 ligands disclosed as filed does not appear to provide sufficient enablement for a genus of distinct molecules of antigens" / "proteins" other than the known CD40 ligands relied upon applicant's disclosure as filed.

Further, it is noted that co-inventor's Noelle's related application USSN 08/742,480 was party to an Interference from the United Stated Patent and Trademark Office Board of Patent Appeals and Interferences (Interference No. 104,415). See Noelle v. Lederman, 69 USPQ2d 1508 (CAFC 2004), relied upon by applicant in the amendment, filed 9/23/05.

Although the Decision in Noelle v. Lederman was directed towards written description and not enablement, the following is noted.

With respect to the disclosure of antibodies that bind a genus of CD40 ligand/gp39/CD40CR antigens, the Court affirmed the decision by the Board supported by substantial evidence and the law which held that the USSN 08/742,480 application lacked written description for the genus of CD40CR antigens, including human CD40CR antigen (see Decision, including pages 1508-1509, 1516-1517)

Given the state of the art in the early 1990's described by the expert witnesses and evidence, the Court also affirmed the decision by the Board by finding that one skilled in the art would have lacked a reasonable likelihood of success in isolating human CD40CR antigen given mouse CD40CR antigen, including consideration of Noelle's reliance on various screening methods disclosed in the specification (see Decision, including pages 1516-1517).

Applicant has not disclosed "a fully characterized antigen" / "protein" as it reads on "antigens" / "proteins" other than the known CD40 ligands at the time the invention was made.

Since the amino acid sequence of a polypeptide determines its structural and functional properties, predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain similar functionality (e.g. ligand or receptor) requires a knowledge of and guidance with regard to which amino acids in the polypeptide's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which a polypeptide's structure relates to its functional usefulness. However, the problem of predicting polypeptide structure from mere isolation of a single protein and, in turn, predicting structural elements (e.g. amino acid or encoding nucleic acid sequences) to provide for a genus of "antigens" / "proteins" that have the appropriate structural and functional characteristics of this genus of molecules is complex and well outside the realm of routine

experimentation. In re Fisher, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

In the absence of sufficient guidance and direction to the structural and functional analysis of a sufficient number of species, the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue to make and use the genus of "antigens" / "proteins" other than the particular CD40 ligands identified by the instant disclosure as filed and known by the skilled artisan at the time the invention was made.

9. Claims 82-94 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 82-94 are indefinite in the recitation of "(iii) has the same molecular weight as a protein precipitated by the CD40-Ig fusion protein" in that they only describe the "protein" of interest by its ability to "precipitated by a CD40-Ig fusion protein". While this "limitation" itself may have some notion of the activity of the protein, there is nothing in the claims which distinctly claims the "protein". Applicant should particularly point out and distinctly claim the "protein precipitated by the CD40-Ig fusion protein" by claiming sufficient characteristics associated with the protein (e.g. activity, molecular weight, amino acid composition, N-terminal sequence, etc.). Claiming biochemical molecules by a particular name given to the protein by various workers in the field fails to distinctly claim what that protein is and what the compositions are made up of.

In consideration of the discrepancies often encountered in the art between protein molecular weight when determined by different methods, when a molecular weight is recited to characterize a protein the claims should include not only the method by which it was determined, e.g. whether by sodium dodecyl sulphate polyacrylamide gel electrophoresis, gel filtration or some other method, but also whether the determination was made under denaturing or non-denaturing conditions and whether reducing or non-reducing conditions were are used.

Further, the claimed "antigen" is described in terms of "(iii) a protein" in a relative manner which renders the claim indefinite. The "protein" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

Applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter. See MPEP 714.02 and 2163.06

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office Action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 82-94 are rejected under 35 U.S.C. ɜ 103 as being unpatentable over Lederman et al. (U.S. Patent No. 6,403,091) in view of Berschorner et al. (U.S. Patent No. 5,597,563), Cobbold et al. (U.S. Patent No. 5,690,933) and Enyon et al. (J. Exp. Med. 175: 131-138, 1992) and added back references Armitage et al. (U.S. Patent No. 6,264,951) OR Aruffo et al. (U.S. Patent No. 6,376,459) of record to address applicant's newly added claims to address the limitations CD40-Ig fusion proteins for the reasons of record.

As noted in the previous Office Action, mailed 12/3/04, Armitage et al. (U.S. Patent No. 6,264,951) OR Aruffo et al. (U.S. Patent No. 6,376,459) were withdrawn from the previous rejection of record, given applicant's amended claims that delete the use of soluble CD40 and soluble CD40 fusion proteins in the claimed methods.

Given applicant re-introduction of limitations encompassing "CD40-Ig fusion proteins", the teachings of Armitage et al. (U.S. Patent No. 6,264,951) OR Aruffo et al. (U.S. Patent No. 6,376,459) have been similarly re-introduced into the record.

The following teachings of Armitage et al. (U.S. Patent No. 6,264,951) OR Aruffo et al. (U.S. Patent No. 6,376,459) are of record (e.g. see the Office Actions, mailed 10/22/02 and 7/28/03).

Armitage et al. teach the use of CD40 antagonists, including CD40/Fc to teat conditions associated with high levels of antigen-antibody complexes including SLE, rheumatoid arthritis and IDDM (see columns 10-11, overlapping paragraph) (see entire document).

Aruffo et al. teach the use of CD40CR antagonists such as CD40Ig and CD40CR-specific antibodies such as MR1 (Section 5.1) to prevent or ameliorate a subject suffering from a disorder associated with B cell activation, including autoimmune conditions, such as SLE and rheumatoid arthritis (Section 5.4, particularly, column 16, paragraphs 1-2 and column 17, paragraph 1 and Section 5.5 and Claims) (see entire document).

The following is a reiteration of the previous Office Action for applicant's convenience.

Applicant's arguments of record have been fully considered but are not found convincing essentially for the reasons of record.

Applicant's arguments and the examiner's rebuttal are essentially the same of record.

Applicant argued that the prior art did not provide sufficient motivation and expectation of success at the time the invention was made for the claimed methods.

Applicant argued that Enyon's T cells are not activated and therefore do not express gp39 and therefore is irrelevant to any tolerization process involving T cells expressing gp39 since there would be no need to administer an activated T cell inhibitors if T cells never became activated in the first place due to the lack of co-stimulatory signal. Applicant further asserted that the tolerance taught by Enyon requires the use of an adjuvant and that temporary tolerance as described would be fairly worthless from a therapeutic perspective. Applicant asserted that given the teachings of Enyon, there would be no motivation to administer an anti-gp39 antibody.

Again it was noted that Enyon et al. teach that B cell presentation of antigen in the absence of appropriate help leads to antigen-specific T cell anergy in vivo (see entire document). Here, Enyon et al. also acknowledge the art-known role of B cells as APCs, including B cell involvement in tolerance induction in skin graft survival (see page 131, column 2, paragraph 1). Enyon et al. also note that antigen-specific B cells are involved in tolerance induction (page 132, column 1, lines 11-17).

In contrast to applicant's assertions concerning the limitations of Enyon, the teachings of Enyon et al. are not limited to specific therapeutic regimens. Rather, Enyon et al. does provide sufficient motivation and expectation of success that B cells, including both antigen-specific B cells and small resting B cells can serve as antigen presenting cells in tolerizing regimens. Enyon et al. also teach a role for small B cells as antigen-specific tolerizing antigen-presenting cells in acquired self-tolerance soluble self-proteins (see Abstract and last paragraph of Discussion).

Given that Berschorner's tolerization process is based on depletion of dendritic cells (APCs) in the thymic medulla using an immunosuppressant followed by recruitment or infusion of new APCs to thymus while treating with various stimulating growth hormones, applicant argued that anti-gp39 antibody would have deleterious effects on Berschorner's tolerization process. Applicant assertions that Berschorner teaches away from the claimed methods since Bershcorner's methods of not administering an immunosuppressant along with APCs were in direct contravention to the presently claimed methods and further asserts that both methods are mutually exclusive of one another.

Again, Berschorner teach the use of antigen containing antigen-presenting cells for inducing tolerance to autoantigens or self antigens in the treatment of autoimmune diseases by administering the said antigen containing antigen presenting cells and an immunosuppressive (see entire document, including Detailed Description and Claims). Beschorner also teach that the antigen presenting cells include dendritic cells, Langerhans cells and mononuclear phagocytes (see column 6, paragraph 3), encompassed by the claimed methods. While Berschorner is direct to a goal of inducing antigen-specific tolerance while minimizing risk to the animal that is normally associated with protracted immunosuppressive therapy, it is noted that Berschorner acknowledges that immunosuppressive therapy was the standard therapy at the time the invention was made (see Background of the Invention and Summary of the Invention).

Applicant argued that Cobbold's teachings are irrelevant to anti-gp39 antibodies, since these teachings cannot be extrapolated to antibodies against any T cell antigen, particularly to antibodies that inhibit gp39, which were believed to only inhibit T cell's activation of a B cell.

Again, Cobbold et al. teach that specific non-responsiveness can be induced to a self antigen or antigens in order to treat autoimmune diseases by administering immunosuppressive antibodies and antigen (see entire document, including column 3, paragraph 4). Cobbold et al. also note that persistent antigen is require to maintain tolerance, which applies to self (auto) antigens in the treatment of autoimmune diseases (column 3, paragraph 5). Cobbold et al. teach antigen presenting cells can be isolated from the bone marrow, blood, thymus, epidermis, liver, fetal liver or spleen (see column 6, paragraph 3). In contrast to applicant's assertions, Cobbold et al. provides direction to inducing tolerance via the inhibition of T cells. Furthermore, the CD40L was not known at the priority date of Cobbold et al.

Applicant argued that the each and every one of the anti-gp39 antibodies have any effect on T cell responsiveness and asserted that these references only teach anti-gp39 antibodies may reduce B cell activation.

In contrast to applicant's assertions, Lederman et al. provides for methods for inhibiting the rejection of transplant organs (see column 11, paragraph 6 and Claims) in a subject with 5c8-specific antibodies (i.e. CD40 ligand- / gp39-specific antibodies) in addition to methods of the autoimmune response (see column 11, paragraph 7).

Applicant submitted that the combination of references is incongruent and fails to teach the methods of the present claims.

Contrary to applicant's assertions that teachings of Enyon, Beschorner and Cobbold do not support a general conclusion that APCs can be administered to induce tolerance with gp39-specific antagonists with sufficient motivation and expectation of success at the time the invention was made, the following of record was noted for applicant's convenience.

It was also known that CD40 the ligand for gp39 (CD40 ligand) is present on other APCs such as dendritic cells, which are intimately involved in the induction of T cell immunity or tolerance. In addition, gp39 was known to be expressed mainly by activated T helper cells and a number of $CD8^+$ cells as well. Therefore, it was known that one could use gp39 antagonists to block T cell-mediated activation and that the appropriate in vivo APCs such as B cells and dendritic cells, which express CD40, would be subject to such manipulation. It was well known in the art at time the invention was made that the provision of signal 1 (antigen) in the absence of signal 2 (help) would lead to some form of tolerance rather than immunity.

With respect to applicant's request for the support that "it was well known in the art at the time the invention was made that the provision of signal 1 (antigen) in the absence of signal 2 (help) would lead to some form of tolerance rather than immunity", applicant is invited to look no further than the Background of the Instant specification, including page 2, paragraph 1.

As indicated above, applicant acknowledges that APCs can provide antigen to induce tolerance or specific non-responsiveness in various contexts and systems at the time the invention was made.

Contrary to applicant's assertions, the prior art provide sufficient motivation and expectation of success that providing an immunosuppressive regimen, including antagonistic antibodies, in combination with APCs can induce tolerance or antigen-specific nonresponsiveness.

Here, the teachings of Lederman et al. clearly provide for anti-CD40L (anti-5c8, anti-gp39, anti-CD40 ligand) antibodies to inhibit the immune response in order to treat various disease conditions, such as autoimmunity. These teachings are consistent with the teachings of Enyon, Beschorner and Waldmann to provide APCs to induce tolerance to antigens of interest under the cover of immunosuppression at the time the invention was made.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. In re McLaughlin, 170 USPQ 209 (CCPA 1971). References are evaluated by what they suggest to one versed in the art, rather than by their specific disclosures. In re Bozek, 163 USPQ 545 (CCPA 1969).

In response to applicant's arguments that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See In re Fine 5 USPQ2d 1596 (Fed. Cir 1988) and In re Jones 21 USPQ2d 1941 (Fed. Cir. 1992).

In this case the teachings of the primary references pertaining to the treatment of disease conditions such as autoimmunity and the teachings of the secondary references indicating the success of employing APCs to induce tolerance or specific antigen to solve a similar problem of treating autoimmunity would have led one of ordinary skill in the art at the time the invention was made to combine the references to solve a well known problem in the art of inducing long term non-responsiveness to autoantigens in such individuals having autoimmunity. The strongest rationale for combining reference is a recognition, expressly or implicitly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent that some advantage or expected beneficial result would have been produced by their combination In re Sernaker 17 USPQ 1, 5-6 (Fed. Cir. 1983) see MPEP 2144

A prior art reference may be considered to teach away when "a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." In re Gurley, 31 USPQ2d 1130, 1131 (Fed. Cir. 1994). General skepticism of those in the art -- not amounting to teaching away -- is also "relevant and persuasive evidence" of nonobviousness. Gillette Co. v. S.C. Johnson & Son, Inc., 16 USPQ2d 1923, 1929 (Fed. Cir. 1990). In effect, "teaching away" is a more pointed and probative form of skepticism expressed in the prior art. In any case, the presence of either of these indicia gives insight into the question of obviousness.

A prior art reference may be considered to teach away when "a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." See In re Gurley , 31 USPQ2d 1130, 1131 (Fed. Cir. 1994).

Here in contrast to applicant's assertions of teaching away by the prior art because the references are directed to alternative tolerance induction regimens, there is insufficient discouragement nor skepticism in the prior art for employing various antigen presenting cells, including those known in the prior art and encompassed by the claimed methods, in the induction of tolerance to antigens of interest, including autoantigens. Furthermore, various immunosuppressive regimens associated with tolerance induction regimens were known and practiced at the time the invention was made to achieve this highly desirable goal.

Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to select the combination of an autoantigen containing antigen presenting cells and a gp39-specific antibody to induce antigen-specific non-responsiveness to autoantigens as a treatment for autoimmunity by providing persistent autoantigens under the cover of immunosuppressives, since both contribute to long term antigen non-responsiveness in the treatment of autoimmunity.

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments have not been found persuasive.

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

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